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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,636	04/17/2001	Srikanth Venkatraman	IN01155K	7298

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SCHERING-PLOUGH CORPORATION
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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,636	VENKATRAMAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicants' election (paper No. 6, filed 3/6/02) of Group 7 with traverse is acknowledged (Claims 1-23 and 26, limited to subgenus G7) Also acknowledged is the elected specie.

The elected specie is a stereoisomer of the first compound listed in claim 27.

Claims 1-23, 26-31 are examined in this Office action.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23, 26, 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions, or to a method of making such. Claims 22 and 26 assert that disorders "associated with HCV protease" can be successfully treated by administering the claimed compounds. As it happens, none of these claims is enabled.

Applicants have demonstrated only inhibition of HCV NS3/NS4a serine protease. It is stipulated that such inhibition will occur *in vivo*. But that does not, in and of itself, translate

into an effective therapy of a hepatitis infection. A key issue is whether the NS3/NS4a protease can be inhibited to a sufficient degree to cause an actual reduction in population of the virions. Issues such as proper anatomical localization, bioavailability, susceptibility of the claimed compounds to proteases and monooxygenases would have to be addressed. For example, if the virus is replicating at a rate of 100 "units" per day in the absence of the compound, and 90 units per day in the presence of the compound, one could say that inhibition had been achieved. However, if the virus is replicating at a rate of 90 per day in spite of the presence of the compound (of claim 1), the patient's condition will still worsen, and "treatment" will not have been achieved. As it happens, structure/activity relationships are unpredictable. As observed by Tung (WO 98/17679), compounds within that disclosed genus (table 9, pp. 106-107) exhibited more than a 100-fold range of efficacies in the inhibition of HCV NS3 protease. Many of those compounds characterized as exhibiting an inhibition above 100 *micro*molar may have been completely inactive. (See also table I of WO 99/07734). Thus, one question is, can applicants look at a structure and determine its activity, even *in vitro*? And if not, how can applicants make predictions about what will happen *in vivo*? As stated in Ingallinella (*Biochemistry* **37**, 8906, 1998) at page 8906, col 1:

"Neither an effective therapy for hepatitis C-associated chronic hepatitis nor a vaccine for preventing HCV infection has... been developed.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, effective treatment of viral infections such as hepatitis cannot be predicted from *in vitro* data alone; undue experimentation would be required to practice the claimed invention. It is suggested that the term "pharmaceutical" be deleted at every occurrence; either of the following could be used:

> *A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.*
>
> *A composition comprising a pharmaceutically acceptable carrier in combination with a compound of claim 1 in an amount effective to inhibit hepatitis C nonstructural protein-3 protease (HCV NS3 protease)*

If deemed appropriate, the following claim can be added:

> *A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) comprising administering a compound according to claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.*

If there is descriptive support for it, the following claim could be added:

> *A method of of inhibiting hepatitis C virus replication comprising administering a compound of claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.*

*

Claims 1-23, 26-31 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 could be interpreted as simultaneously requiring the presence of enantiomers, steroeoisomers, rotomers, tautomers, salts and solvates, i.e., that the claim does not encompass just a single compound. (See also claim 27). If this is not intended, it is suggested that the language be revised. The following format is suggested:

A macrocylic compound of formula I,

{formula I as recited}

or an enantiomer, steroeoisomer, rotomer, or tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof... [etc]

In claim 1, on page 202, line 4, the following is recited:

"alkyl carbamate... halogen, hydroxyl amino, alkyl carbazate"

Here, the term "hydroxyl amino" is somewhat ambiguous. It is suggested that applicants do either of the following, depending on intentions: (a) insert a comma after "hydroxyl", or (b) make the term *hydroxylamino* one word, rather than two.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. §102(a) as being anticipated by Marchetti (*Synlett (Spec.)*, 1000-1002, 1999).

Marchetti discloses compound 3. This compound anticipates a compound within the claimed genus when the substituent variables correspond as follows:

R3 = $HOOC\text{-}CH_2\text{-}CH_2\text{-}$
Z = N
R4 = H
W = >C=O
Y = $\text{-}CH_2\text{-}$ which is "substituted" with alkylamido
X = aryl ether (specifically, biphenyl ether)
A = $\text{-}CH_2\text{-}$
E = absent
G = $\text{-}(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = $\text{-}CH_2\text{-}SH$
R1 = -COOH

Thus, the claims are anticipated.

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Fossli (USP 4,956,344).

Fossli discloses the tripeptide pGlu-His-Gly. This compound is encompassed by the claimed genus when the substituent variables correspond as follows:

R3 = H
Z = CH
R4 = H
W = absent
Y = absent
X = absent
A = $-(CH_2)_p$, wherein "p" is zero
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = NH
V = CH
R2 = H
R1 = COR5
R5 = $N(R^9)R^{10}$
R9 = H
R10 = $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$
R11 = H
R2' = H
R1' = alkylheteroaryl (i.e., the side chain of histidine)

Thus, the claims are anticipated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER